REMARKS

Claims 1-45 were rejected under 35 U.S.C. § 112, first paragraph. Claims 7, 8, 17, 22, 23, 35, and 36 were rejected under 35 U.S.C. § 112, second paragraph. Claims 1-45 were rejected under 35 U.S.C. § 103(a). Each of these rejections is addressed as follows.

Amendments

Claims 6, 8, 10, 21-23, 25, 27, 34-36, 38, and 40 have been canceled. Claims 1, 5, 11, 16, and 33 have been amended to include a recombinant Sendai virus. Claims 4, 20, and 33 have been amended to recite intranasal administration. New claims 46-61 have been added. Support for these claims is found in the instant specification, e.g., page 19, last line to page 20, line 10, and page 32, line 3 to page 34, line 28. No new matter has been added.

Rejections under 35 USC 112, first paragraph

Claims 1-45 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a "Sendai virus expressing a viral protein of an immunodeficiency virus, particularly a virus encoding a gag or gag-pol fusion protein for inducing a specific immune response via intranasal administration and/or combined with a DNA vector expressing the genome of the immunodeficiency virus" does not reasonably provide enablement for "vaccination with Sendai virus via any route of

administration." Applicants disagree.

As an initial matter, Applicants note that only claims 5-10 and 20-45 specifically encompass *in vivo* therapy yet the Examiner has rejected all pending claims as lacking enablement on the noted grounds. Applicants believe that this is improper.

Because claims 5, 20, and 33 have been amended to require an intranasal route of administration, this basis of the rejection may be withdrawn.

Claims 1, 2, and 16 are directed to compositions that are clearly enabled by Applicants' specification. The Office asserts, however, that the claims are unpatentable, in essence, because of overbreadth. On the question of claim breadth, Applicants note that these claims need not include language reciting a method of administration. The Office does not question the sufficiency of Applicants' disclosure on how to make and use the claimed invention. Instead, the Office relies on Ourmanov and McCluskie for a general teaching of "the importance of route of administration with the type of immune response induced."

Applicants' specification enables the scope of the claims 1, 2, and 16. All of the methods needed to practice the invention are taught in Applicants' specification. Furthermore, Applicants note that the Office provides no evidence substantiating its point that the invention of claims 1, 2, and 16 would require undue experimentation. Given Applicants' teachings and results, Applicants' specification cannot be found as failing to enable the claimed invention when the techniques required to practice the invention are

disclosed in the specification and available to those skilled in the art. See In re Wands, *858 F.2d* 731, 740, 8 U.S.P.Q.2d 1400, 1406; In re Strahilevitz, 668 F.2d 1229,1232, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982).

In addition, the Office further contends that the specification fails to teach:

1) whether the SeV-SIV-Gag induced changes in CD8+ cells is sufficient to elicit a protective response against SHIV;
2) whether SeV-SIV-Gag alone (without a previous DNA vaccine encoding the viral protein of HIV or SIV) could achieve any protective effect against SHIV in either monkeys or humans; and
3) whether the protective effect obtained in the DNA-RNA combination regimen is attributed solely or predominantly to the DNA vaccine.

Regarding the Office's specific contentions, it is important to note the pending claims do not expressly require the generation of "a protective response against SHIV." Rather, the claims require the induction of "a cellular immune response specific to [a] virus protein [of an immunodeficiency virus]." Applicants' data clearly supports this limitation.

As evidence of this assertion, Applicants direct the Examiner's attention to the findings discussed in Example 4, where SeV/SIVgag vaccinated cynomogolus macaques were intravenously challenged with a large dose of live SIV virus (SIVmac239). The plasma viral loads in the immunized macaques eventually fell to below detectable levels while those in the control macaques remained as high as 10^5 copies/ml (see Figure 4). Thus, Applicants' data clearly demonstrated the ability of a Sendai viral vector to alone elicit a protective response *in vivo* against an immunodeficiency virus.

Moreover, Applicants submit that SIV is substantially analogous to HIV and SHIV in terms of viral structure and pathogenesis and sufficiently representative of the class of viruses claimed (e.g., immunodeficiency viruses). In fact, the Examiner's own reference, Flanagan *et al.*, states that: "Simian immunodeficiency virus (SIV) infection of macaques has proven to be an important animal model for vaccine development against human immunodeficiency virus (HIV)." Thus, a finding of efficacy of a particular vaccine against SIV reasonably correlates to efficacy of the same vaccine against SHIV and HIV, particularly in light of the exhaustive data presented by Applicants regarding the ability of the SeV/SIVgag vaccine to generate specific cellular responses *in vitro* (Example 3) and systemic immune responses *in vivo* (Examples 6-9).

The Office has failed to present specific evidence to the contrary that casts doubt on the Applicants' claims of efficacy and utility. As stated in In re Marzocchi, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In a situation such as this one and absent evidence to the contrary, Marzocchi compels withdrawal of the enablement rejection, and Applicants request reconsideration on this issue.

In view of the above remarks, Applicants respectfully request that the Patent Office reconsider and withdraw the rejections under § 112, first paragraph, and find that Applicants' specification enables the invention as presently claimed.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 7, 8, 17, 22, 23, 35, and 26 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 7 stands rejected as indefinite on the basis that the phrase "inoculated at least once in multiple vaccine inoculation" and the assertion by the Office that it is "unclear whether the claims encompass or exclude the art." Applicants have amended claim 7 to overcome this rejection.

Claim 17 stands rejected on the basis of improper antecedent basis. This rejection has been met by the present amendment and may be withdrawn.

With the cancellation of claims 8, 22, 23, 35, and 36, the remainder of this rejection is moot.

The § 112, second paragraph rejections may be withdrawn

Rejections under 35 U.S.C. § 103(a)

Claims 1, 2, 5-10, 16-18, 20-45 were rejected under 35 U.S.C. § 103(a) for being obvious over Flanagan et al. (J. Gen. Virol. 78:991-7, 1997) or Seth et al. (PNAS 95:10112, 1998), in view of Hurwitz et al. (Vaccine 15:533-40, 1997). Claims 1-10 and 16-45 under 35 U.S.C. § 103(a) for being obvious over Flanagan or Seth, and Hurwitz, further in view of Yu et al. (Genes Cells 2:457-66, 1997). Claims 11-13 and 15 were rejected under 35 U.S.C. § 103(a) for being obvious over Flanagan and Seth, in view of Kast et al. (J Immunol 140:3186-93, 1988) and Yu. And finally, claims 11-15 were rejected under 35 U.S.C. § 103(a) for being obvious over Flanagan, Seth, Kast, and Yu, in view of Boutillon (U.S. Pat. No. 6,015,564).

In order to establish a *prima facie* case of obviousness based on a combination of references, the Patent Office must show some teaching, suggestion, or incentive supporting the combination. In re Geiger, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987) (citing ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)). Thus, the Examiner must identify something in the prior art which somehow suggests combining the references to produce the claimed invention. The suggestion to combine the references does not need to be expressly stated in one or all of the references. Cable Elec. Prods., Inc. v. Genmark, Inc., 770 F.2d 1015, 1025, 226 U.S.P.Q. 881, 886 (Fed. Cir. 1985). However, in order to determine whether the suggestion to combine exists, the court must determine whether or

not the combined teachings of the prior art, taken as a whole, suggest the combination to one of ordinary skill in the art. In re Napier, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995) (emphasis added). Thus, in order to determine whether or not the teachings of the prior art references are combinable, each reference must be considered in its entirety, and portions arguing against or teaching away from the claimed invention must be considered. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 448, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986); W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1550-51, 220 U.S.P.Q. 303, 311 (Fed. Cir. 1983). In other words, "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." In re Wesslau, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Additionally, prior art references cannot be combined or modified to establish a *prima facie* case of obviousness if their combination or modification would destroy the intended purpose or function of the references. In re Gordon, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). Contrary to the Office's assertions, one of ordinary skill in the art could not have been motivated to combine the teachings of any of the cited references because the teachings of these references are antithetical, as illustrated in detail below.

Flanagan or Seth, in view of Hurwitz

The Office has rejected claims 1, 2, 5-10, 16-18, and 20-45 under 35 U.S.C. § 103(a) for being obvious over Flanagan or Seth, in view of Hurwitz.

Flanagan is cited for teaching the use of an adenovirus expressing SIV gag to achieve long lasting immune response in mice. The Office acknowledges that Flanagan does not teach the use of a Sendai virus vector nor the use of a gag-pol fusion protein as claimed. To cure these deficiencies, the Examiner relies on Seth and Hurwitz; Seth for teaching a vaccinia virus vector expressing gag-pol fusion polypeptides and Hurwitz for teaching a Sendai virus vaccine expressing hPIV-1.

As an initial matter, Applicants disagree with the Office's analysis of Hurwitz. Contrary to the Office's suggestion, Hurwitz does **not** describe a "Sendai vector expressing hPIV-1." Rather, Hurwitz describes a trial involving the infection of monkeys with live **wild-type** Sendai virus. Hurwitz expressly states that the Sendai virus "merits consideration as a candidate for a human vaccine [against hPIV-1] as it is closely related to hPIV in sequence and structure." (see p. 533, col. 1, lines 5-8). Furthermore, "Sendai virus (a mouse PIV-type 1) was chosen for vaccine study, because of its close similarity to hPIV-1." (see p. 539, col. 1, lines 1-2). Nothing in Hurwitz suggests the construction of a **recombinant** Sendai viral vector expressing a foreign protein, much less the construction of a Sendai viral vaccine expressing a specific immunodeficiency virus antigen as claimed. Accordingly, Hurwitz teaches away from the claimed invention. As

a "useful general rule," the Federal Circuit has indicated that "references that teach away cannot serve to create a prima facie case of obviousness." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1131, 1132 (Fed. Cir. 1994).

Moreover, the teachings of Hurwitz are limited to PIV and cannot be extrapolated to the treatment of other viruses, particularly those viruses that are **nonanalogous** to PIV, such as the immunodeficiency viruses SIV, HIV, and SHIV. Accordingly, to the extent that the Office relies upon Flanagan and Seth to establish that it would have been obvious to use a recombinant Sendai virus, merely because it would be obvious to try such an experiment, the Office is in error. *See* Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367, 231 U.S.P.Q. 81, (Fed. Cir. 1986) *cert. denied*, 480 U.S. 947 (1987). ("Obvious to try" is improper consideration in adjudicating obviousness issue.) What is needed for obviousness is a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

In contrast to Hurwitz, Flanagan and Seth used adenovirus and vaccinia virus as vectors, rather than virus itself as a vaccine. When a virus is used as a vector, induction of immune response by viral antigen is an unfavorable event.

To clarify that the Sendai virus vector of this invention is not wild-type, Applicants have amended the claims to recite "recombinant Sendai virus vector."

Accordingly, one skilled in the art would not have been motivated to replace the viruses of Flanagan and Seth with Sendai virus taught by Hurwitz. Indeed, the references

do not contain the requisite motivation needed to combine their teachings to support the Office's conclusion of obviousness. Even if the primary references and the secondary reference are combined, the combined teachings would result in the adenovirus or vaccinia virus vector expressing Sendai virus genome. In sum, Applicants submit that one skilled in the art would not have been motivated to combine the teachings of the Hurwitz disclosure with those of Flanagan and/or Seth to arrive at the claimed invention. Accordingly, the Office's reasoning that one would have been motivated by Flanagan and Seth to change adenovirus and vaccinia virus to recombinant Sendai virus is clearly erroneous.

Flanagan and Seth, and Hurwitz, in view of Yu

The Office has rejected claims 1-10 and 16-45 under 35 U.S.C. § 103(a) for being obvious over Flanagan and Seth, and Hurwitz, in view of Yu.

Flanagan, Seth, and Hurwitz are discussed above. Yu is cited to cure the deficiencies of Flanagan, Seth, and Hurwitz. Yu is cited for teaching the deletion of the V gene to increase expression of viral protein. As noted above, the Sendai virus utilized by Hurwitz is the **wild type** Sendai virus. Hurwitz does not describe the construction of a **recombinant** Sendai vector, much less a Sendai viral vaccine vector expressing foreign proteins such as vaccine antigens.

The Office pointed out that the adenovirus vector of Flanagan and the vaccinia

virus vector of Seth are DNA vaccines (page 5, line 2 up and page 6, line 13 of the Office Action). One skilled in the art would not have been motivated to replace DNA virus taught by Flanagan and Seth with Sendai virus that is an RNA virus taught by Yu.

Furthermore, Sendai virus is superior to adenovirus and vaccinia viruses in that only a small dose can produce a sufficient vaccine effect due to its high expression level of a transgene and that infectivity to the nasal cavity is high. Such superior effects of the claimed invention would not have been obvious from any of the cited references.

Because the teaching of Yu does not cure the deficiencies of Flanagan, Seth, and Hurvitz, this § 103(a) rejection also lacks support and should be withdrawn.

Flanagan and Seth, in view of Kast and Yu

The Office has rejected claims 11-13 and 15 under 35 U.S.C. § 103(a) for being obvious over Flanagan and Seth, in view of Kast, further in view of Yu.

The Flanagan, Seth, and Yu references are discussed above. Kast is cited for teaching the transfection of dendritic cells with Sendai virus.

Kast, like Hurvitz, does not describe a **recombinant** Sendai viral vector or its use in expressing a foreign protein, such as a vaccine antigen. Rather, Kast describes the use of live **wild type** Sendai virus as an antigen to induce immune response. The instant invention uses Sendai virus as a vector and it is unfavorable to induce an immune response by a Sendai viral antigen itself. Accordingly, Kast teaches away from the

claimed invention of a recombinant Sendai viral vector encoding a virus protein of an immunodeficiency virus. Because the Kast teaching does not cure the deficiencies of Flanagan, Seth, and Yu, this § 103(a) rejection also lacks support and should be withdrawn.

In sum, one skilled in the art would not have been motivated to combine the teachings of the Kast disclosure with those of Yu, Flanagan and Seth to arrive at the claimed invention.

Flanagan, Seth, Kast, and Yu, in view of Boutillon

The Office has rejected claims 11-15 under 35 U.S.C. § 103(a) for being obvious over Flanagan, Seth, Kast, and Yu, in view of Boutillon.

According to the Examiner, Boutillon teaches using herpes virus papio transforming B lymphoblastoid cells for CTL assay. As discussed above, one skilled in the art would not have been motivated to combine Flanagan or Seth, with Kast and Yu. Because the disclosure of Boutillon does not cure the deficiencies of Flanagan, Seth, Kast, and Yu, this § 103(a) rejection also lacks support and should be withdrawn.

For all of the aforementioned reasons, applicants respectfully submit that the cited references fail to support a *prima facie* case of obviousness, and § 103(a) rejections should be withdrawn.

CONCLUSION

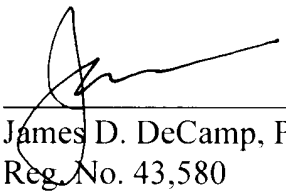
Applicants submit that this case is in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition for Extension of Time and a check in the amount of $930.00 for the required fee. A Submission of Extension Fee for $460.00 is also enclosed. And finally, enclosed is a check in the amount of $72.00 for the newly added dependent claims.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 31 JULY 2003



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